REMARKS

After entry of this amendment, claims 51-99 are currently pending in the instant application. Claims 1-50 have been canceled without prejudice. Applicants reserve the right to prosecute any canceled subject matter in one or more continuation or divisional applications.

Correspondence between original claims 1-50 and new claims 51-99 is shown below:

Original Claims	New Claims
13+21	51
22	52
23	53
24	54
25	55
26	56
14	57
15	58
16	59
17	60
18	61
19	62
20	63
49	64
50	65
41 (in part)	66
-	67
-	68
-	69
-	70
-	71
-	72
-	73
-	74

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-	75
-	76
-	77
-	78
-	79
-	80
42	81
43	82
44	83
27	84
28	85
29	86
30	87
31	88
32	89
33	90
34	91
35	92
36	93
37	94
-	95
-	96
38 (in part)	97
39 (in part)	98
40 (in part)	99

Original claims 1-12 and 45-48 have been canceled with no new counterparts. The subject matter of the amended claim recitations is fully supported in the specification and claims as originally filed. In particular, support for the amended recitation of claims 67-80, 95 and 96 can be found throughout the specification, *inter alia*, at page 28, paragraph 1. No new matter has been added.

Claim Objections

Claims 30-48 are objected to as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim.

Original claims 30-48 have been canceled. The corresponding new claims contain no multiple dependencies; thus, this objection is obviated with respect to these claims.

Rejections under 35 U.S.C. §112, Second Paragraph

Claim 10 is rejected under 35 U.S.C. §112, second paragraph as being indefinite for the recitation "claim9".

Claim 10 has been canceled; thus, this rejection is obviated with respect to this claim.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 6 and 23 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement for failing to comply with all the requirements for deposit of biological material under 37 C.F.R. §§ 1.801 *et seq*.

In response, submitted herewith is a Statement by Attorney for Applicants Regarding Deposited Biological Material, with a copy of the original depository receipts. The specification has also been amended at pages 8-9 to recite that the deposit was made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedures, and the provisions of 37 C.F.R. §§ 1.801 et seq.

In light of the above, it is submitted that this rejection with respect to these claims has been overcome.

Claims 27 and 29 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. According to the Examiner, the specification does not reasonably provide enablement for all cancers. Further, the Examiner contends that undue experimentation would be required by one skilled in the art to use the instant invention to treat all types of cancer.

In response to the rejection of claims 27 and 29 (new claims 84 and 86) for lack of enablement, Applicants respectfully disagree. Applicants submit that the specification contains sufficient teaching to enable one skilled in the art to practice the full scope of the invention without undue experimentation. Applicants direct the Examiner's attention to Heider *et al.* Cancer Immunol. Immunother. (1996) 43:245-253 (cited on page 3, paragraph 3 of the specification) which states that "expression of CD44v6 was detected in basically all types of carcinomas investigated" (page 252, lines 8-10). Further , Applicants respectfully direct the Examiner's attention to Example 1.2, page 32 "Analysis of *in vitro* binding of BIWI 1" of the specification which describes binding of a conjugate of the invention to a human head and neck cancer cell line (FaDu). Thus, expression patterns in various cancers can be determined using methods well-known in the art, for example, immunohistochemistry. Applicants further direct the Examiner's attention to Example 1.3, pages 32-33 and Figure 1 which describes an *in vitro* cell cytotoxicity assay using a conjugate of the invention and two cancer cell lines, FaDu and A431 (epidermoid carcinoma of the vulva) and to Examples 2.2-2.4, pages 33-35 and Figures 2-4 which describe *in vivo* efficacy of a conjugate of the invention for treating various cancers. In addition, Applicants direct the Examiner's attention to Examples 2.6-2.10, pages 36-47 and Figures 6 and 7 which describe *in vivo* efficacy of a compositions of the invention, *i.e.*, a conjugate of the invention in combination with various chemotherapeutic agents, for treating various cancers. Thus, screening of cancers and determination of efficacy of a composition of the invention for treating cancer are fully enabled by the specification. Applicants submit that the description contained in the specification enables a person skilled in the art to carry out the invention. Accordingly, Applicant request that the rejection of claims 27 and 29 for lack of enablement be withdrawn.

Applicants submit that in view of the amendments and remarks, all of the rejections under Section 112, first paragraph have been overcome and must be withdrawn.

Statutory Double Patenting

Claims 1-12 and 21-25 are provisionally rejected under 36 U.S.C. §101 as claiming the same invention as that of claims 1-18 of co-pending Application No. 10/150,475 (US 2003/0103985) ("the '475 Application").

Claims 1-12 have been canceled in the instant application thereby rendering this rejection moot with respect to these claims. Claims 21-25 (new claims 51-55) of the instant application are directed to composition comprising *a chemotherapeutic agent and* a conjugate of a CD44v6 specific antibody molecule and a maytansinoid. Claims 1-12 of the '475 Application have been canceled, thereby rendering this rejection moot with respect to these claims. Claims 13-18 of the '475 Application are directed to a conjugate of a CD44v6 specific antibody molecule and a maytansinoid. Applicants submit that in light of the above amendments, this provisional rejection for statutory double patenting has been overcome and must be withdrawn.

Obviousness-type Double Patenting

Claims 26-29 (new claims 56 and 84-86, respectively) are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-26 and 31-36 of the '475 Application.

As a preliminary matter, Applicants point out that claims 31 and 34 of the'475 Application have been canceled thereby rendering this rejection moot with respect to these claims.

Claims 19-26, 32, 33, 35 and 36 of the '475 Application are directed to a conjugate of a CD44v6 specific antibody molecule and a maytansinoid, wherein the maytansinoid has the Formula IV (claims 19-26) and to methods of treating cancer comprising administering a conjugate of a CD44v6 specific antibody molecule and a maytansinoid (claims 32, 33, 35 and 36). As discussed above, claims 26-29 (new claims 56 and 84-86, respectively) are directed to compositions comprising a conjugate of a CD44v6 specific antibody molecule and a maytansinoid *and a chemotherapeutic agent* and to methods of treating cancer comprising administering a conjugate of a CD44v6 specific antibody molecule and a maytansinoid *in combination with a chemotherapeutic agent*. Applicants submit that in light of the above amendments, this provisional rejection for obviousness-type double patenting have been overcome and must be withdrawn.

Claims 1 and 4-6 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 and 8-12 of U.S. Patent No. 5,916,561 ("the '561 Patent").

Applicants point out that clams 1 and 4-6 in the instant application have been canceled with no new counterparts thereby rendering this rejection moot with respect to these claims.

Applicants submit that in light of the above remarks and amendments, all of the rejections under the judicially created doctrine of obviousness-type double patenting have been overcome or obviated and must be withdrawn.

Rejections under 35 U.S.C. §102

Claims 1, 4-6 and 28 are rejected under 35 U.S.C. §102(b) as being anticipated by the '561 Patent.

Claims 1, 4-6 and 28 are rejected under 35 U.S.C. §102(b) as being anticipated by Heider *et al.*, Cancer Immunol Immunother. (1996) 43:245 ("Heider *et al.*").

Claims 1, 4-6 and 28 have been canceled. In light of the above amendments, Applicants respectfully submit that the rejections based on Section 102(a) have been obviated and must be withdrawn.

Rejections under 35 U.S.C. §101

Claims 28 and 29 are rejected under 35 U.S.C. §101 as being indefinite for merely reciting a use without any active, positive steps delimiting how the use is actually practiced.

Claims 28 and 29 (new claims 85 and 86) have been amended to be more in conformance with U.S. practice. The recitation "use" of claims 28 and 29 has been replaced by proper method terminology which finds inherent support throughout the specification as filed.

Applicants respectfully submit that in view of the above amendments and remarks, the rejection of claims 28 and 29 (new claims 85 and 86) under 35 U.S.C. §101 have been overcome and must be withdrawn.

Rejections under 35 U.S.C. §103

Claims 1 and 4-7 are rejected under 35 U.S.C. §103(a) as being obvious over the '561 Patent.

Claims 1 and 4-6 are rejected under 35 U.S.C. §103(a) as being obvious over Heider *et al.*

Claims 1-29, 49 and 50 are rejected under 35 U.S.C. §103(a) as being obvious over WO 01/24763 in view of Heider *et al.* or the '561 Patent and Applicants' admission on pages 22+ of the specification.

As a preliminary matter, Applicants point out that claims 1-12 have been canceled with no new counterparts thereby making these rejections moot with respect to these claims.

The Present Claims

Claims 13-29, 49, and 50 (now claims 51-65 and 84-86) are specifically directed to a composition comprising a chemotherapeutic agent and a conjugate of a CD44v6 specific antibody molecule and a maytansinoid (new claim 51 and new claims 52-65 dependent thereon);and a method of treating cancer comprising administering a compound comprising a conjugate of a CD44v6 specific antibody molecule and a maytansinoid of Formula IV in combination with a therapeutic agent (new claim 84 and claims 85 and 86 dependent thereon).

The Cited References

According to the Examiner, WO 01/24763discIsocs immunoconjugates comprising at least one therapeutic agent for killing selected cell populations linked to a cell binding agent in combination with a chemotherapeutic agent. The Examiner indicates that the targeting agent in the cited reference differs from that of the instant application.

According to the Examiner the '561 Patent discloses monoclonal antibody VFF-18 and linking of the antibody to toxins, prodrugs and radioactive substances, The '561 Patent generically disclose toxins, but does not specifically describe maytansinoids. Further, the '561 Patent does not specifically disclose compositions comprising a chemotherapeutic agent and a conjugate of a CD44v6 specific antibody molecule and a maytansinoid.

According to the Examiner, Heider *et al.* disclose monoclonal antibody VFF-18 linked to ^{125}I, which is a toxin and its reaction with squamous cell carcinomas. In contrast the compositions of the instant application are directed to a *chemotherapeutic agent and* a conjugate of a CD44v6 specific antibody molecule and a *maytansinoid*.

Non-Obviousness of the Present Claims

The Examiner contends that the subject matter is obvious in view of prior art disclosing CD44v6 specific antibodies (Heider *et al.* or the '561 Patent) or antibody maytansinoid conjugates wherein the disclosed antibodies are specific for a different target antigen as the antibody of the present invention (WO 01/24763). According to the Examiner, it would have been obvious to apply the maytansinoid conjugate approach to anti-CD44 antibodies, as this would merely be replacing the antibodies of the prior art by a CD44 specific antibody.

Applicants submit that while WO 01/24763 discloses the combination of an anti-CD56 antibody maytansinoid conjugate with certain chemotherapeutic drugs, the application of the conjugate disclosed in this reference is restricted due to the limited expression of the respective target antigen. The antigen recognized by N901 (CD56, N-CAM) is predominately expressed by tumors of neuroendocrine origin, *e.g.* in small cell lung cancer.

Thus, the need to overcome this limitation by finding efficient drugs applicable in a different or broader spectrum of tumors still exists. The present invention provides a solution to this problem. This solution is the combination of anti-CD44 antibody maytansinoid conjugates with chemotherapeutic drugs. Applicants submit that it was not obvious to combine these two partners because the choice of one of the partners, the anti-CD44 antibody conjugate, as an anti-cancer agent as such is non-obvious.

The human CD 44 gene is expressed as a number of different splice variants which comprise several variant exons to a differing extent. The exon CD44v6, as well as other variant exons (CD44v, CD44v5, CD44v7/v8, and CD44v10) has been shown to be a tumor-associated antigen with a favourable expression pattern in human tumors, and has, therefore, been suggested as a target for antibody-based cancer therapy.

However, it was far from obvious to choose anti-CD44 antibodies for the maytansinoid conjugate approach because this approach is based on the concept that the conjugate-antigen complex is internalised into the target cell. Within the cancer cell, maytansinoid is cleaved from the conjugate and then the free maytansinoid kills the cell because it is much more toxic than the uncleaved conjugate (see Chari *et al.*, 1992, Cancer Res. 52:127-131, therein page 127, left column, last paragraph; page 128, left column, Results and Discussion section). A prerequisite for efficient killing of tumor cells by antibody-maytansinoid conjugates therefore is sufficient internalization of the target antigen into the cell. This mechanism is different from the way an antibody linked to a radioisotope (for example, ^{125}I) would work. It is sufficient for ^{125}I to simply bind to the surface of the target cell.

Whether an antigen-antibody complex is internalised into a cell depends on the nature of the antigen and the biological mechanisms controlling its fate. Besides being internalised and degraded, a cell surface antigen may leave the cell surface by a process called shedding. Altogether, "[i]nternalization processes are poorly understood and difficult to influence" (Chari *et al.*, loc. cit.). Applicants submit that the skilled artisan would not have expected that CD44 is sufficiently internalised by cancer cells at all, and therefore would not have considered anti-CD44 antibodies as promising candidates for the maytansinoid conjugate approach. Before the present invention, only few data on the internalization of CD44 were available. Bazil and Horejsi reported that down-regulation of CD44 on leukocytes upon stimulation with PMA is caused by shedding of the antigen rather than by internalization (Bazil V and Horejsi V. Shedding of the CD44 adhesion molecule from leukocytes induced by anti-CD44 monoclonal antibody simulating the effect of a natural receptor ligand. J Immunol 149 (3):747-753, 1992). Shedding of CD44 is also supported by several reports on soluble CD44 in the serum of tumor patients and normal individuals (Guo

YJ *et al.* Potential use of soluble CD44 in serum as indicator of tumor burden and metastasis in patients with gastric or colon cancer. Cancer Res 54 (2): 422-426, 1994.; Martin S, Jansen F, Bokelmann J, and Kolb H. Soluble CD44 splice variants in metastasizing human breast cancer. Int J Cancer 74 (4): 443-445, 1997.).

Taken together, these data suggest that CD44 receptors are more likely subject to shedding than to internalization, and thus CD44 specific antibodies are not to be regarded as suitable candidates for the maytansinoid conjugate approach. It was then unexpectedly found by the present inventors that anti-CD44 maytansinoid conjugates were effective anti-tumor agents. Therefore, this feature make the subject matter of the present invention, the combination of anti-CD44 maytansinoid conjugates with chemotherapeutic agents non-obvious.

Furthermore, the present invention demonstrates unexpected supra-additive effects of the combination of the individual components. Applicants respectfully direct the Examiner's attention to Example 2.7, pages 37-41 and Example 2.8, pages 41-44 of the specification where such supra-additive effects are disclosed. The fact that others have obtained unexpected results for a different combination does not render such an effect for the instant combination obvious because it is absolutely impossible to extrapolate from one antibody acting on a certain target antigen present in certain target cells to another antibody acting on a totally different antigen present in different cells, *i.e.*, in a different biological setting and different cancer type. There is no mechanistic rationale for such an extrapolation. The expert knowing the teaching of WO 01/24763, therefore, would not have expected *a priori* that such effects could be achieved for a different antibody conjugate as the underlying mechanisms of such an effect are unknown. Thus, WO 01/24763, alone or in combination with the other cited references, would not afford one of ordinary skill in the art motivation to combine anti-CD44 maytansinoid conjugates with chemotherapeutic agents much less a suggestion and reasonable expectation that the combination of anti-CD44 maytansinoid conjugates with chemotherapeutic agents has therapeutic utility for the treatment of cancer.

With respect to all the presently pending claims, Applicants submit that for all the reasons detailed above, the cited references cannot and do not make obvious the

claimed conjugates, methods or pharmaceutical compositions. Accordingly, all the rejections based on Section 103 must be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that all of the objections and rejections have been overcome and must be withdrawn. Further, Applicants submit that the application is now in form for issuance and an early allowance is earnestly requested. If any issues remain, the Examiner is invited to telephone the Attorney at the number below.

Respectfully submitted,

Date: January 18, 2005

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